A careful review of Applicants' response mailed January 23, 2004 (at page 2 thereof) expresses Applicants' understanding that the Examiner's request to identify a species of assay for initial examination (spectroscopy was the species selected) is only an election of species (37 CFR 1.146) and not a requirement of restriction (37 CFR 1.142). Therefore, upon indication of allowability of the species invention, Applicants will be requesting rejoinder of all other species of assay (claims 26-55, Group I, drawn to method of identifying an organic non-peptide compound, classified in class 436, subclass 91). If indeed, the Examiner was requesting restriction, then Applicants' remarks in response thereto should clearly be understood as a traversal thereof.

Applicants respectfully believe that the Office has not yet had time to evaluate the major scope and pioneering nature of the presently claimed invention. Reference is made to the numerous documents of record in the file of the parent '542 application which hopefully can be considered, albeit that file is quite lengthy. In summary of the present invention, Applicants have made the pioneering discovery that small organic compounds, present in *doses that are small and safe enough to be administered to living patients*, can successfully rescue the conformation of p53 protein in order to facilitate treatment of cancer. This breakthrough discovery is in complete contrast to the art-recognized approach of gene therapy, which has not yielded any success. The present inventors prominently published their discoveries (Science, v. 286, pp. 2507-2510, of record herein), and it reasonably appears that numerous pharmaceutical companies promptly began to screen as taught by the Applicants. The following further serves as a summary of the present invention and its background.

The function of p53 protein and related proteins of the p53 family

It is well accepted that wild-type p53 functions as a transcriptional regulator to coordinately control multiple pathways in cell cycling, apoptosis, and angiogenesis. Loss of p53 function can lead to uncontrolled proliferation of cells and tumor growth. Although loss of p53 activity may or may not, by itself, be the trigger to transforming a cell into a cancer cell, it is well recognized that detectable cancers are more common and likely to grow in persons with p53 mutations. In fact, mutants of p53 are the most common genetic aberration for many types of cancer (specification at page 1). As is elaborated in detail on page 2 of the specification, p53 activity is highly dependent upon the ability of the protein to maintain its functional conformation. However, analysis of p53 from the cells of many tumors reveals that the DNA binding domain thereof is frequently mutated. Specific residue positions in p53, known as hot spots, are mutated at unusually high frequencies in cells evidencing major cancer (specification at page 2).

Generally speaking, mutant p53 proteins are not as stable as wild type protein, having shorter effective lifetimes and/or less inherent regulatory activity. In the current state of the art, efforts have focused on replacing such defective p53 protein molecules by gene therapy in order to provide a wild-type encoding nucleotide sequence. The present Specification discloses a completely different approach demonstrating, for example, that small molecule drugs can rescue a functional conformation in defective p53.

The present invention thus has broad implications for cancer therapy. In the text of the present application, Applicant has provided actual data from an art-recognized *in vivo* model (suppression of human tumor cells transplanted into nude mice) clearly showing operability of the invention. See, for example, page 12 of the application referring to Figure 6, showing testing of compound "X", N-{2-[2-(4-Methoxy-phenyl)-vinyl]-quinazolin-4-yl}-N',N'-dimethyl-propane-1,3-diamine hydrochloride. The species referred to as compound "X" is depicted in Figure 2 of the Specification, and is also the subject of *in vivo* model Example 4 (pages 49-50), and Figures 5 and 6 (see pages 11-12)..

Applicant has thus demonstrated that the conformation of mutant p53 can be stabilized by administration of an organic non-peptide compound. With respect to compound X, Applicant has further demonstrated that stabilizing the conformation of mutant p53 results in enhanced p53 function (Example 3 on page 47). Referring to pages 41 and 49-50 of the Specification, p53 possesses an epitope recognized by monoclonal antibody mAb1620. The epitope is conformation-dependent, and the epitope's presence correlates strongly with p53's tumor suppressor activity. In Example 4 (page 49-50), Applicant demonstrated that p53 function can be stabilized in human tumor cells that express mutant p53, and which are being cultured in nude mice. Figure 6 demonstrates that human tumor xenografts (in nude mice) can be suppressed by administration of a compound useful in the practice of the invention. The tumor cells express mutant p53, and upon administration of compound, tumor volumes decrease. Simply stated, Applicants have provided very remarkable experimental results, which are now published at Science, v. 286, pp. 2507-2510, and Cancer Biology and Therapy, Internet pre-published on September 4, 2001 as Manuscript MS# 08-08-01 (note that the compound identified therein as CP-31398 is compound X of the present application).

The Section 102 and 103 rejections

Upon review of the Official Action mailed June 3, 2004, it appears that the only major rejections that have been lodged against the claims are those presented under 35 USC section 102 (Welch et al., 5,900,360), and under 35 USC section 103 (Das et al. in combination with Welch et al). Since the rejections are readily traversed, they should be dealt with first.

The present invention defines methods (see independent Claim 26) which include the obvious practical limitation that the identified compounds are actually "useful in the treatment of cancer" and can usefully bind to p53 under physiological conditions. Compound X (Example 3, page 47) is such a compound.

The Welch disclosure is readily seen as being not particularly relevant to the discovery of compounds that are useful as drugs, particularly those that likely bind to specific sites in the p53 protein. Rather the Welch disclosure relates to the well recognized field that proteins can be solubilized or "stabilized" by soaking in them in solvents, at immense concentrations of solvent, and usually via generalized solvation effects.

While the Welch disclosure contains numerous examples ***in vitro*** of loading up cells with well known solvents and stabilizing agents (glycerol and TMAO, and the like) where apparently the cells don't lyse (at least for a while), this has absolutely nothing to do with providing binding-specific compounds useful as safe, low dose pharmaceuticals. For example (see column 26 of the '360 patent), in order to evaluate alleged folding properties of p53, the cells were immersed in 0.6 Molar glycerol, more than enough (36 grams/liter of body mass) to pickle the patient and preserve his or her body forever; ditto essentially for the 75mM TMAO. Nor is suspending cells in culture media reconstituted in pure deuterated water predictive of anything. The deuteron has different pKa properties than the regular hydrogen proton, and the changes in effective pK of all bodily enzymatic reactions throughout an entire person soaked in 100% deuterated water is actually predictive of only one thing, a very painful death. Thus, general solvation effects requiring 0.1 to 18Molar concentration of solvents have nothing to do with specific binding effects of compounds that are operable at **clinically useful sub micromolar quantities**. Simply stated, the generalized history of protein solvation experiments has nothing to do with the development of useful pharmaceuticals, nor can it, in any way, **provide motivation for such other inventions or even remotely suggest predict that such useful inventions would be remotely possible**. Welch fails, as it must, to suggest specific binding effects useful at physiological concentrations. It must be reiterated that the cells in patients' living bodies are very different from the cells in the *in vitro* cultures of Welch -- the patients must survive the experiment.

There being no disclosure or motivation present in the Welch reference that can be applied to the present invention, the Das et al. reference adds nothing. Of course, the present Applicants' claims embrace assay methodology and steps that may be new or old, but the motivation to use those steps for the presently claimed purposes is not provided in the art. The present Applicants do not claim to be the first persons to aim a fluorimeter at a protein. It is thus seen that the present invention, immensely pioneering as it is, is fully patentable.

Remaining Rejections

Applicants are in the process of cross checking and compiling the cited Form 1449 references that are apparently missing from the files of co-pending 09/443,542.

Applicants agree to correct (and will so do by an immediately following paper) the informalities (see pages 2-3 of the Official Action) in the Claims and Specification.

In regard of monoclonal antibodies mAB 1620 and 240, an appropriate reference to publicly available and maintained hybridomas will be inserted.

The Examiner has also noted a few instances of lack of proper antecedent basis for terms in the claim set (section 112, second paragraph, see Page 7 in the Official Action), and Applicants agree to correct all such instances.

Conclusion

An early and favorable reply is respectfully requested. The Examiner is welcome to contact the undersigned to resolve any remaining issues. A Petition for Extension of Time (three months, in duplicate) is attached.

Respectfully submitted,

Date: 12/3/04

E. Victor Donahue, Ph.D.
Attorney for Applicant(s)
Reg. No. 35,492

Pfizer, Inc
Patent Department, 5th Floor
150 East 42nd Street
New York, NY 10017-5755
(212) 733-2739